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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,927	01/29/2009	Sek Chung Fung	Case 1050 US	4825

26839 7590 02/28/2011

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
02/28/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,927	FUNG ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *96-107 and 110-155* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *118,119,124,125,129-131,133 and 135* is/are allowed.

6)☒ Claim(s) *96-107, 110-117, 120-123, 126-128, 132, 134, and 136-155* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090925;20101213*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*

DETAILED ACTION

1. Applicant's election filed December 13, 2010, is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has elected the invention of Group IV, claims 62-75 and 82-85, drawn to a DNA sequence encoding a heavy or light chain of an antibody or fragment thereof that binds to human IL-13, a vector comprising said DNA sequence, and a host cell comprising said vector.

In addition, Applicant has elected the species of the invention of Group I, wherein said antibody comprises a CDRH1 having the amino acid sequence of SEQ ID NO: 117, a CDRH2 having the amino acid sequence of SEQ ID NO: 123, a CDRH3 having the amino acid sequence of SEQ ID NO: 135, a CDRL1 having the amino acid sequence of SEQ ID NO: 99, a CDRL2 having the amino acid sequence of SEQ ID NO: 104, and a CDRL3 having the amino acid sequence of SEQ ID NO: 115.

2. The amendment filed December 13, 2010, is acknowledged and has been entered. Claims 70-75, 77, 78, 80-95, 108, and 109 have been canceled. Claims 96-107 have been amended. Claims 110-155 have been added.

3. Claims 96-107 and 110-155 are pending in the application and are currently under prosecution.

Information Disclosure Statement

4. The information disclosures filed September 25, 2009, and December 13, 2010, have been considered. An initialed copy of each is enclosed.

Notably, the disclosure statement filed December 13, 2010, lists "Search Reports". The listing of the references cited in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR

1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Priority

6. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing dates of international application PCT/US04/43501, filed December 23, 2004, which claims benefit of Provisional Application No. 60/532,130, filed December 23, 2003, is acknowledged.

However, claims 96-107 and 110-155 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those

claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

Accordingly, the effective filing date of the claims is deemed the filing date of the international application PCT/US04/43501, namely December 23, 2004.

Drawings

7. The drawings set forth as Figures 11, 12, 15, 18, and 19 are objected to because the figures depict amino acid sequences, which are not identified by sequence identification numbers, either in the figures or in the brief descriptions of figures at page 7. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the figure at page 4 of the specification to include sequence identification numbers.

8. The drawings are objected to because Figure 11 includes portions labeled A, B, C, and D, but its brief description does not provide a description of the separate portions thereof; and similarly, Figure 12 includes portions labeled A, B, C, C, and D but its brief description does not provide a description of the separate portions thereof.

Furthermore, Figure 21 includes portions labeled A and B, but its brief description does not provide a description of the separate portions thereof.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Appropriate correction is required.

Specification

9. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figures 11, 12, 15, 18, and 19 are not identified by sequence identification numbers, either in the figures or in the brief descriptions of figures at page 7.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

10. The specification is objected to because the Brief Description of the Drawings fails to comply with 37 CFR 1.84(p)(5) which requires every reference character to be described in the brief description.

In this instance, as noted above, Figure 11 includes portions labeled A, B, C, and D, but its brief description does not provide a description of the separate portions thereof; Figure 12 includes portions labeled A, B, C, C, and D but its brief description does not provide a description of the separate portions thereof; and Figure 21 includes portions labeled A and B, but its brief description does not provide a description of the separate portions thereof.

Claim Objections

11. Claims 102 and 103 are objected to as being drawn in the alternative to the subject matter of a non-elected species of invention.

12. Claims 99, 107, 113, 115, 136, and 137 are objected to because claim 99 uses "(ii)" twice.

13. Claims 98, 100, 101, 104-105, 110, 111, and 120-123 are rejected herein as being specifically directed to a deposited material, where the referral to a deposit of the deposited material at, for example, page 50 of the specification is insufficient assurance

that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) are met, so as to satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph; see 37 C.F.R. §§ 1.801-1.809. Notably, if this rejection that follows were obviated by the provision an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, *as explained below,* these claims would still then be objected to as being dependent upon a rejected base claim. So, in the interest of advancing prosecution, it is noted that once this rejection is obviated by the provision of such an affidavit or declaration, these claims could be placed in condition for allowance if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Claim 138 is objected to because the claim erringly depends from claim 18 (as opposed to claim 118).

Claim Rejections - 35 USC § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 116, 117, 126-128, 132, 138-155 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 116, 117, 126-128, 132, 138-155 are indefinite for the following reasons:

Claims 116 and 117 are drawn to "a humanized antibody of an antibody produced by a hybridoma", but it cannot be ascertained what structural properties need be attributed to the claimed antibody such that it is dubbed "a humanized antibody of an

antibody produced by a hybridoma". Must it comprise a heavy and light chain variable region comprising the six complementarity determining regions (CDRs) of which the antibody produced by the hybridoma is comprised to be regarded a "humanized antibody" of the antibody produced by the hybridoma? According to dependent claims 120 and 121, this might be the case – but, since claims should be given the broadest, reasonable interpretation, it appears that the claimed "humanized antibody" of the antibody produced by the hybridoma is not necessarily an antibody having such a defined structure. What structural attributes characterize the claimed "humanized antibody then? Because of this fact it is submitted that the claim cannot be unambiguously construed such that that skilled artisan would be reasonably apprised of the metes and bounds of the subject matter that is regarded as the invention. Accordingly, it is submitted that the claim fails to delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. §112, second paragraph.

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 96-107, 110-117, 120-123, 126-128, 132, 134, and 136-155 are directed to an antibody, which is derived from an antibody produced by a hybridoma cell line deposited under ATCC accession number PTA-5657.

The referral to a deposit of the hybridoma at, for example, page 50 of the specification is insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) are met, so as to satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph; see 37 C.F.R. §§ 1.801-1.809.

Notably, the specification discloses that the deposit of this hybridoma producing the antibody to which the claims are directed was made under the provisions of the Budapest Treaty and that this "assures permanent and unrestricted availability of the

progeny of the culture to the public upon issuance of the pertinent U.S. patent" (page 50). However, as to the specific matter of the conditions by which the deposited materials is made available, this disclosure is factually incorrect since the Treaty leaves this to the discretion of each State[1]. Consequently, the mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty does not satisfy the requirement that all restrictions on access be removed on grant of the patent. *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Therefore, since a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. *Again, as prescribed by national law, this requirement is necessary when deposits are made under the provisions of the Budapest Treaty, as indeed the Treaty leaves this specific matter to the discretion of each State.*

19. Claims 96-107, 110-117, 120-123, 126-128, 132, 134, and 136-155 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a polynucleotide encoding a heavy chain or a variable heavy chain region of an antibody that specifically binds to human Interleukin-13 (IL-13) and a polynucleotide encoding a light chain or a variable light chain region of an antibody that specifically binds to human Interleukin-13 (IL-13), wherein said antibody comprises a light chain variable region comprising complementarity determining regions (CDRs)

[1] According to M.P.E.P. § 2404.01: Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all

having the amino acid sequences of SEQ ID NO: 99, SEQ ID NO: 104, and SEQ ID NO: 115 and a heavy chain variable region comprising CDRs having the amino acid sequences of SEQ ID NO: 117, SEQ ID NO: 123, and SEQ ID NO: 135, **does not reasonably provide enablement for making and using** the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the

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restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are drawn to nucleic acid molecules (polynucleotides) encoding polypeptides comprising particular portions (i.e., a heavy chain polypeptide or a portion thereof – namely the heavy chain variable region; or a light chain polypeptide or a portion thereof – namely the light chain variable region) of an antibody. Accordingly it follows that in general, if the skilled artisan is to be able to make (and use) the claimed invention, the structure of the claimed antibody must be known or determinable.

According to the disclosure the claimed antibody is not necessarily a monoclonal antibody but may instead be a polyclonal antibody produced by methods are known to the skilled artisan, but in particular using those described in a 1988 publication by Harlow, et al; see, e.g., paragraph [0057] of the published application[2]. However, the methodology described by Harlow et al. is not methodology that might be used to produce the claimed antibody that comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, CDRH3 having the sequences of SEQ ID NOs: 117, 123, and 135, respectively, and wherein said antibody comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, CDRL3 having the sequences of SEQ ID NOs: 99, 104, and 115, respectively. Instead, it is submitted that the methodology known to the skilled artisan as of the filing date sought in this application by Applicant, as represented by that which is described by Harlow et al. in 1988, might be used to produce a plurality of different species of antibodies, as is the nature of a "polyclonal antibody", which binds to different epitopes of human IL-13 and which have markedly different structures comprised of substantially disparate heavy and light chain variable regions. Then, too, even if one were to use very recently developed methods of recombinantly producing polyclonal antibodies[3], it is noted that these methods would not necessarily be expected to produce antibodies having the particular structural features of the claimed antibody but would be expected to produced a plurality of structurally disparate antibodies. Accordingly, it is submitted

[2] U.S. Patent Application Publication No. 2011/0014199-A1.

that at best the specification would only be reasonably enabling for producing nucleic acid molecule encoding a portion (e.g., a heavy chain) of a *monoclonal* antibody that specifically binds to human Interleukin-13 (IL-13), wherein said antibody comprises a light chain variable region comprising complementarity determining regions (CDRs) having the amino acid sequences of SEQ ID NO: 99, SEQ ID NO: 104, and SEQ ID NO: 115 and a heavy chain variable region comprising CDRs having the amino acid sequences of SEQ ID NO: 117, SEQ ID NO: 123, and SEQ ID NO: 135.

Turning to a different issue, in the case of claims 96 and 97 (and dependent claims) the claimed antibody is an antibody that "comprises antigen-binding regions derived from an anti-IL-13 antibody comprising the amino acid sequence of an antibody produced by a hybridoma designated with [ATCC] accession number PTA-5657". Since "antigen-binding regions" of which the claimed antibody are comprised are not defined with any of the requisite clarity and particularity to permit the skilled artisan to immediately envision its structure, it is submitted that the claimed invention cannot be made (or used) without undue and unreasonable experimentation. This is in part because, while the "antigen-binding regions" must be *derived from* an anti-IL-13 antibody comprising the amino acid sequence of an antibody produced by a hybridoma deposited under ATCC accession number PTA-5657, they need not have any particular structure; as such, the claims are directed to an antibody that binds human IL-13, which is somehow derived from another antibody that also binds to human IL-13, but which need not have or share any of the structural features that account for the ability of the antibody produced by the hybridoma to bind to human IL-13. The skilled artisan cannot predict whether any given derivative of an antibody lacking certain structural features of an antibody from which it was derived, as is later discussed in detail below, will have or retain the capability of specifically binding to the antigen to which the latter antibody binds. For this reason, the claimed antibody cannot be made without undue and unreasonable experimentation and neither can the claimed polynucleotide that encodes particular portions (i.e., a heavy chain polypeptide or a portion thereof – namely the

[3] See, e.g., Rasmussen et al. (*Biotechnol. Lett.* 2007 Jun; **29** (6): 845-852).

heavy chain variable region; or a light chain polypeptide or a portion thereof – namely the light chain variable region) of the claimed antibody.

In contrast to claims 96 and 97, claims 98 and 99 (and dependent claims, at least in part) are directed to an antibody, which although also *derived from* an anti-IL-13 antibody comprising the amino acid sequence of an antibody produced by a hybridoma deposited under ATCC accession number PTA-5657, must comprise the six complementarity determining regions (CDRs) of the which the light and heavy chain variable regions of the antibody produced by the hybridoma is also comprised. As discussed in further detail below, such an antibody certainly includes, for example, a CDR-grafted antibody in which the CDRs of a parental antibody (usually a murine antibody) are transplanted into the framework of the variable regions of heterologous light and heavy chain polypeptides (typically human in origin); such a CDR-grafted antibody (e.g., a "humanized" antibody) having the six CDRs of the which the light and heavy chain variable regions of the antibody produced by the hybridoma is comprised is reasonably expected to have or retain the antigen binding specificity of the latter antibody.

However, if any one or more of the CDRs of which the light and heavy chain variable regions of the antibody produced by the hybridoma is comprised is omitted from the derivative thereof, the consequences upon antigen binding specificity are unpredictable – but in general such a derivative is not be expected to have or retain the antigen binding specificity of the antibody from which it was derived. This limitation in the field of recombinant antibody engineering is discussed in greater detail in the paragraphs that follow.

Claims 116 and 117 (and dependent claims, at least in part) are directed to an antibody that binds human IL-13, which is "a humanized antibody of the antibody produced by a hybridoma" deposited under ATCC accession number PTA-5657. Since according to claims 120 and 121, the humanized antibody of claims 116 and 117 comprises a CDRL1, a CDRL2, and a CDRL3 having the amino acid sequences of SEQ ID NOs: 99, 104, and 115, respectively, and a CDRH1, a CDRH2, and a CDRH3 having the amino acid sequences of SEQ ID NOs: 117, 123, and 135, respectively, it stands to

reason that the humanized antibody according to claims 116 and 117 need not comprise light and heavy chain variable regions comprising the six complementarity determining regions (CDRs) of the antibody produced by the deposited hybridoma - Applicant is reminded that claims are given the broadest, reasonable interpretation that is consistent with the specification and since, here, there is a presumption that claims 120 and 121 properly limit the subject matter to which claims 116 and 117 are directed, claims 116 and 117 are construed as being directed to an humanized version of the antibody produced by the deposited hybridoma, including any version that does not comprise each and every one of the CDRs of which the antibody produced by the hybridoma is comprised.

Therefore it is again submitted that if any one or more of the CDRs of which the light and heavy chain variable regions of the antibody produced by the hybridoma is comprised is omitted from the derivative thereof, the consequences upon antigen binding specificity are unpredictable – but in general such a derivative is not be expected to have or retain the antigen binding specificity of the antibody from which it was derived. This limitation in the field of recombinant antibody engineering is discussed in greater detail in the paragraphs that follow.

Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition is reviewed. A naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

The prior art teaches well-known and conventional methodology for "humanizing" monoclonal antibodies. For example, Gussow et al. (*Methods in Enzymology*. 1991; **203**: 99-121) teach the general methodology for making humanized antibodies; see

entire document. One means for producing a humanized antibody involves grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

De Pascalis et al. (*J. Immunol.* 2002; 169 (6): 3076-3084), for example, describes demonstrating by CDR grafting that, while perhaps not directly contacting the antigen, certain framework residues are essential to the preservation of the structural integrity of the antigen binding site; see entire document (e.g., page 3079, column 2).

Having realized the role of the framework residues, Wu et al. *(J. Mol. Biol.* 1999 Nov 19; **294** (1): 151-162) discloses the finding that it is difficult to predict which framework residues serve critical roles in maintaining the antibody's affinity and specificity, due in part to the large conformational change that occur in the antibody upon its interaction with the antigen; see entire document (e.g., page 152, column 1).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by the disclosure, for example, of Casset et al. (*Biochem. Biophys. Res. Commun.* 2003 Jul 18; **307** (1): 198-205). Casset et al. describes the rational design and construction of a peptide mimetic of an anti-CD4 monoclonal antibody binding site; see entire document (e.g., the abstract). The peptide mimetic was designed with 27 residues formed by inclusion of residues from five of the six CDRs of the antibody; see, e.g., the abstract. Casset et al. states that although the heavy chain CDR3 is at the center of most, if not all antigen interactions, clearly other CDRs play an important role in the recognition process; see, e.g., page 199, column 1. This conclusion is apparent given their demonstration that an active peptide mimetic that retains the ability to bind to the antigen necessarily comprises amino acids derived from all CDRs, except the light chain CDR2, in addition to a framework residue located just before CDR3 of the antibody's heavy chain; see, e.g., page 202, column 1. Though Casset et al. concedes that perhaps not all of the residues representing the various different CDRs will ultimately prove essential to the interaction, it will not be without further extensive studies that such a realization may be made (page 202, column 1).

Then too it is further noted that the art of engineering functional recombinant antibodies, such as the grafted antibodies to which the claims are directed, is even more confounded by findings that residues, which are positioned outside the recognized boundaries of the canonical CDRs, may contribute substantially to the interaction of an antibody and an antigen. For example, MacCallum et al. (*J. Mol. Biol.* 1996 Oct 11; **262** (5): 732-745) describes the discovery that although the residues of CDR3 of the heavy and light chains are dominant determinants of the interaction, a number of essential residues contacting the antigen have been placed outside the regions that are

recognized using the conventional or standard definitions of the CDRs, which are generally used to define the components of the antigen binding site of the antibody; see entire document (e.g., page 733, column 2). Moreover, MacCallum et al. teaches an appreciation of the fact that residues within the CDRs that do not actually make contact with the antigen may be important because of their contributions to the conformation of the antibody's antigen recognition site; see, e.g., page 735, column 1.

Making further apparent the unpredictability of the importance of residues within the CDRs and other parts of an antibody, which must instead be determined empirically, Holm et al. (*Mol. Immunol.* 2007 Feb; **44** (6): 1075-1084) describes the mapping of residues important to the interaction of an anti-cytokeratin antibody with the antigen, where although residues in the CDR3 of the heavy chain were determined to be essential, they disclose their *unexpected* finding that a residue in CDR2 of the light chain forms a necessary part of the antigen binding site of the antibody contacting the antgen; see entire document (e.g., the abstract). Thus, as recently as 2007, there are reports indicating despite the progress made toward understanding the interactions of antibodies and antigens, because of the unpredictable nature of the art, much information concerning the specificity and/or affinity of any given antibody cannot be gleaned by a causal examination and analysis of its structure, but must instead be gathered by rigorous, albeit perhaps routine, experimentation.

Therefore, although the skill of those in the art is relatively high, the claimed antibody (and the claimed invention, namely a nucleic acid encoding part of the antibody) could not be made and used without undue and unreasonable experimentation. This is largely because of the unpredictable consequences of amino acid substitutions, insertions, and deletions in the primary structure of an antibody or portion thereof, so that the effects of such alterations in the structure of an antibody must be tested empirically before the antibody can be used. Again, although it may be well within the skill of the artisan to graft the three CDRs from both the light and heavy chain variable regions of the disclosed antibody into the framework of a human antibody without substantial loss of affinity and specificity, the claims are not limited to such engineered antibodies, since the substitutions, deletions and insertions can occur within

the CDRs; and moreover, the claims encompass antigen binding proteins comprising only a light or heavy chain variable region, but not necessarily both, and broadly (but reasonably) interpreted antigen binding proteins comprising light and heavy chain variable regions that comprise only one or two, and not necessarily all three CDRs of the light and/or heavy chain variable domains of the disclosed, particularly described antibody.

So, inasmuch as the claims should be given the broadest, reasonable interpretation that is consistent with the specification, the claims encompass antibodies that might consist of only a heavy chain variable region or only a light chain variable region. However, this application fails to describe such an antibody consisting of only a heavy chain variable region or only a light chain variable region, but not also the variable region of the other chain, which is capable of binding to a polypeptide designated human IL-13; and it is submitted that one skilled in the art could not make such an antibody without undue and unreasonable experimentation since, for example, such an antibody comprising only one or the other of the light or heavy chain variable region of antibody 228B/C-1 is not expected to have or the ability to bind to human IL-13.

Then, although the claimed antibody *might* comprise both heavy and light chain variable regions, as in accordance to some of the claims, it is not necessary that the claimed antibody always comprise any one or all of the corresponding CDRs of which the heavy and light chains of the antibody produced by the hydridoma is comprised. Since the other variable region of which the claimed antibody might be comprised is not that of the corresponding variable region of the disclosed antibody, and need not comprise any one of the CDRs of which the disclosed antibody produced by the hyridoma is comprised, it stands to reason that the other variable region may not have any structural similarity to that of the corresponding variable region of the disclosed antibody, provided of course that the antibody have the ability to bind to an epitope of human IL-13.

In general, if only one or two of the CDRs from either the light or heavy chain variable region of a given antibody (e.g., the antibody designated herein as "228B/C-1")

were to be grafted into light and heavy chain variable regions having different frameworks, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced relatively early in the development of the art by Rudikoff et al. (*Proc. Natl. Acad. Sci. USA.* 1982; **79** (6): 1979-1983). Rudikoff et al. teaches that the alteration of a *single* amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of, or failure to retain the antigen binding specificity of the "parental" antibody by the variant; see entire document (e.g., the abstract). This sensitivity to such minor alterations is not an anomaly, but rather has since been often been observed a prevalent, if not frequent phenomenon[4].

In summary then, it is submitted that at best the specification only reasonably enables the skilled artisan to make and use a polynucleotide encoding a heavy chain or a variable heavy chain region of an antibody that specifically binds to human Interleukin-13 (IL-13) and a polynucleotide encoding a light chain or a variable light chain region of

an antibody that specifically binds to human Interleukin-13 (IL-13), wherein said antibody comprises a light chain variable region comprising complementarity determining regions (CDRs) having the amino acid sequences of SEQ ID NO: 99, SEQ ID NO: 104, and SEQ ID NO: 115 and a heavy chain variable region comprising CDRs having the amino acid sequences of SEQ ID NO: 117, SEQ ID NO: 123, and SEQ ID NO: 135.

Accordingly, Applicant is duly reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a variant of the disclosed antibody having a structure according to the claims, which has or retains the ability of the disclosed antibody to specifically bind to an IL-13 polypeptide; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

20. Claims 96-107, 110-117, 120-123, 126-128, 132, 134, and 136-155 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

[4] See, e.g., Winkler et al. (*J. Immunol.* 2000 Oct 15; **165** (8): 4505-4514), describing changing the

the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

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specificity of an antibody by single point mutations (entire document; e.g., the abstract).

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In this instance, the claims are directed to a plurality of nucleic acid molecules (polynucleotides) encoding polypeptides comprising particular portions (e.g., a heavy or light chain variable region) of any of a genus of anti-human IL-13 antibodies, including both monoclonal and polyclonal antibodies, which have substantially disparate structures and include variants that may have light or heavy chain variable regions comprising at least one variant CDR that has an amino acid sequence that may vary rather substantially by any number of modifications (i.e., substitutions, deletions, or additions) relative to the amino acid sequence of the corresponding CDR of the disclosed antibody (i.e., "228B/C-1") produced by the deposited hybridoma.

However, for reasons that are evident in view of the teachings of the numerous references cited in support of the above rejection of the claims, as failing to satisfy the enablement requirement set forth under 35 U.S.C. § 112, first paragraph, it is submitted that the instant application would not reasonably convey to the skilled artisan that Applicant had possession of the claimed genus of antibodies (or of the claimed invention, namely a plurality of nucleic acid molecules (polynucleotides) encoding polypeptides comprising particular portions (e.g., a heavy or light chain variable region) of any of this genus of antibodies as of the filing date of the application. Instead it is submitted that at best the instant disclosure would only reasonably convey Applicant's possession as of the filing date of this application of a polynucleotide encoding a heavy chain or a variable heavy chain region of an antibody that specifically binds to human

Interleukin-13 (IL-13) and a polynucleotide encoding a light chain or a variable light chain region of an antibody that specifically binds to human Interleukin-13 (IL-13), wherein said antibody comprises a light chain variable region comprising complementarity determining regions (CDRs) having the amino acid sequences of SEQ ID NO: 99, SEQ ID NO: 104, and SEQ ID NO: 115 and a heavy chain variable region comprising CDRs having the amino acid sequences of SEQ ID NO: 117, SEQ ID NO: 123, and SEQ ID NO: 135.

Applicant is duly reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, as in that, there is no language that adequately describes with the requisite clarity and particularity at least a substantial number of the members of the claimed genus of antibodies having such widely varying structures, which have the ability to bind to a human IL-13 polypeptide. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

It is further noted that Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail in the above rejection of claims as lacking an enabling disclosure, there is in fact such unpredictability in the art of antibody engineering, such that the skilled artisan cannot predict the consequence of structural variations within the amino acid sequences of the CDRs (HVRs) of the heavy and light chain variable regions of antibodies upon their antigen binding specificities and affinities.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a list of structural variants of antibodies known to bind to a human IL-13 polypeptide, which may or may not have or retain this same ability, does not fulfill the written description requirement. This is in part because the

Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to bind to human IL-13, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed invention depends upon finding the structural variants of antibodies known to bind to a human IL-13 polypeptide, which certainly have or retain this same ability; without actual possession or knowledge of the identities of at least a substantial number of the members of the claimed genus of such variants, however, it is impossible to practice the invention (i.e., make and use the claimed polynucleotides, vectors, host cells, or processes that use those host cells to make polypeptides).

In addition, although the skilled artisan could potentially identify the variants having the structural features of the claimed invention that might have the requisite binding specificity by screening pluralities of structurally varying antibodies or fragments thereof to find those having this ability, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate

written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of the structurally varying antibodies to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify the variants having the structural features of the claimed invention that might have the requisite binding specificity.

Finally, Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Moreover, because the claims encompass a genus of antibodies, which are capable of binding IL-13 but which may vary so substantially in their structures, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that

Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

In this case, since the claims are so broad, and the disclosure is so comparably limited, it is submitted that any alleged conception has no more specificity than simply a wish to know the identity of any material with that requisite biological properties.

In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Lastly, since the claims are not necessarily limited to known materials having the functional properties of the claimed antibody that binds to IL-13, but rather to such material that might be identified, given the bid set forth in the instant disclosure to do so, it is noted that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (Bd. Pat. App. & Int. 1993).

Thus, it is submitted that the instant claims, and the disclosure describing the claimed subject matter, fails to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Conclusion

21. Claims 118, 119, 124, 125, 129-131, 133, and 135 are allowable; no other claim is allowed.

22. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Iba et al. (*Protein Eng.* 1998 May; **11** (5): 361-70) teaches changes in the specificity of antibodies by introduction of mutations into complementarity-determining regions of the V(H) domain. Kettleborough et al. (*Protein Eng.* 1991 Oct; **4** (7): 773-83) teaches the importance of framework residues on loop conformation in humanization of a mouse monoclonal antibody by CDR-grafting.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
February 25, 2011